REMARKS

Status of the Claims

Claims 1,2 and 5-18 were pending in the application. Of these, claims 6-18 were withdrawn from consideration. Claims 3-4 were canceled. Claims 1, 2 and 5 are rejected.

Withdrawn claims 6-18 are canceled herein. Claim 1 is amended. Claim 2 is canceled.

The 35 U.S.C. §112, First paragraph , Rejection

Claim 1 remains rejected and newly amended claim 5 is rejected under 35 USC §112, first paragraph for reasons set forth in paper mailed November 5, 2003, Section 7, pages 3-12.

The Examiner maintains the earlier rejections to claims 1 and 5 since the Examiner finds the Applicant's earlier argument to the issues discussed in the previous Office Action unpersuasive. Further, in addition to maintaining the earlier rejections, claims 1 and 5 are rejected for two new reasons. The Examiner contends that the limitation of "humanized anti-HER-2/neu antibody" in the absence of the modifier "monoclonal" before "antibody" and the

limitation of the antibody "that binds to the p185 extracellular domain of HER-2/neu" have no clear support in the specification and the claims as originally filed.

Claim 1 has been amended. Amended claim 1 recites a method of treating uterine serous papillary carcinoma that over-express HER-2/neu. The method comprises the step of administering to an individual with the carcinoma a therapeutically effective dose of humanized murine anti-HER-2/neu monoclonal antibody 4D5 (HERCEPTIN®) that binds to the extracellular domain of HER-2/neu.

The specification teaches that HERCEPTIN® is IgG1k immunoglobulin that contains human framework regions with complementary-determining regions of a murine monoclonal antibody that binds Mr 185,000 extracellular determinant of HER-2/neu (page 18, lines 9-12). When used in flow cytometry analysis, it demonstrated extremely high reactivity against HER-2/neu receptor on uterine serous papillary carcinoma (USPC) cell lines compared to established breast cancer and fresh and established ovarian cancer cell lines (Example 3, Figure 2). The specification further

demonstrates that the uterine serous papillary carcinoma cell lines were significantly inhibited by HERCEPTIN® (Example 14, Table 2) and also that the tumor cells were highly sensitive to HERCEPTIN®-mediated antibody dependent cellular cytotoxicity (Examples 10-13). The Applicant submits that these are clear examples and data that demonstrate and support the use of humanized murine anti-HER-2/neu monoclonal antibody 4D5 (HERCEPTIN®) to treat HER-2/neu over-expressing uterine serous papillary carcinoma. Therefore, the specification has sufficient enablement commensurate in scope with the claimed method. Accordingly, Applicants request that the rejection of claims 1 and 5 under 35 U.S.C. §112 be withdrawn.

Under the new grounds of rejection, the specification stands objected to, and claim 2 rejected, under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public, (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

Claim 2 has been canceled. Therefore, 35 U.S.C. 112, first paragraph rejection of this claim is moot.

The 35 U.S.C. §103 Rejection

Claim 1-2 and 5 remain rejected under 35 USC §103 for the reasons previously set forth in the Paper mailed November 5, 2003, Section 10, pages 14-17. Applicants respectfully traverse this rejection.

The Examiner finds the Applicant's argument regarding teachings of **Bookman et al, (J. Clinical Oncology, 21:283-290)** as unpersuasive. The Examiner contends that **Bookman et al** by demonstrating objective response to HERCEPTIN in 3/41 patients teaches that HERCEPTIN is effective in treating subset of ovarian cancer patients whose tumors over-express Her-2/neu. Additionally, according to the Examiner, **Bookman et al** also teaches the overall tolerability of the treatment regimen. Therefore, the Examiner states that in view of teachings of **Bookman et al** and further reasons of record, it would have been prima facie obvious to one of ordinary skill in the art to treat any epithelial malignancy that is shown to over-express HER-2/neu, including uterine serous papillary carcinoma

with HERCEPTIN. Further the Examiner states that since all of **Berchuck et al, Saffari et al** and **Wang et al** specifically teach that at least a subset of patients with uterine serous papillary carcinoma over-express HER-2/neu, one would have had a reasonable expectation of successfully treating at least a subset of the patients with HERCEPTIN. Applicants respectfully disagree.

Applicants maintain that the teachings of the present invention differs greatly from the teachings of **Bookman et al, Berchuck et al, Saffari et al** and **Wang et al.** In **Bookman et al.**, only 3 of the 41 patients achieved an objective response. Of the 3 patients only one had a complete response while the other two had partial response. In view of these results, a person having ordinary skill in this art would certainly consider this a statistically insignificant, random effect. Clearly, a person having ordinary skill in this art would not have a reasonable expectation that uterine serous papillary carcinoma could be treated with HERCEPTIN®, in view of the fact that 38 out of 41 patients exhibited no response whatsoever to it. Furthermore, **Bookman et al.** state explicitly that based on the low frequency of HER-2 over-expression and very low response rates to

single-agent HERCEPTIN®, it would be practical to combine HERCEPTIN® with platinum based therapy. Obviously, a person having ordinary skill in this art would not expect to treat this disease with HERCEPTIN® alone. Instead, **Bookman et al.** suggests targeting other related signal transduction molecules to increase the proportion of patients that might benefit from a combined therapy approach (page 289, column 2, last paragraph). Therefore, **Bookman et al.** does not teach one with ordinary skill in the art that HERCEPTIN® could be used to treat any epithelial malignancy including uterine serous papillary carcinoma.

With regard to **Berchuck et al.**, **Wang et al.**, and **Saffari et al.**, the Applicants would like to respectfully point out that these studies analyzed only a small number of uterine serous papillary carcinoma samples. In the study undertaken by **Berchuck et al.**, the authors analyzed 12 papillary carcinoma samples out of 95 samples and found only 3 that showed high HER-2/neu staining (page 17, column 2, last paragraph). In the study undertaken by **Wang et al.**, of the two patients with uterine papillary serous carcinoma that were examined for both HER-2/neu and epidermal growth factor

receptor expression, one sample was positive for only HER-2/neu expression whereas the other sample was positive for both (page 2630, column 2, lines 25-29). **Saffari et al.** teach that of the three uterine serous papillary carcinoma cases that were examined only one showed high HER-2/neu expression while the other two showed a low expression of HER-2/neu (page 5694, Table 1). Therefore, for the reasons cited above the three different studies do not teach one with ordinary skill in the art that Her-2/neu is uniformly over-expressed in every uterine serous papillary carcinoma and therefore, could be targeted to successfully treat the disease. Additionally, the teachings of all four cited prior art combined, do not provide one of ordinary skill in the art with any motivation to treat HER-2/neu over-expressing uterine serous papillary carcinoma patient with HERCEPTIN® nor does it provide reasonable expectation of success in treating these patients with HERCEPTIN®.

The present invention, on the other hand, employed both immunohistochemistry and flow cytometry to examine the expression of HER-2/neu expression in uterine serous papillary carcinoma. Of the ten samples that were analyzed by immunohistochemistry in this

study, nine samples showed very heavy staining (3+) (Table 1, page 15). The quantitative results of flow cytometry on cell lines established from three of the nine samples that showed heavy staining for HER-2/neu, also demonstrated HER-2/neu over-expression (Figure 2, Example 3). Further, the specification also teaches the induction of Fc-dependent and -independent mechanisms in the presence of HERCEPTIN® which is not taught by any of the above-cited references to enable HERCEPTIN® to be used as a therapeutic agent in the treatment of uterine serous papillary carcinoma.

Applicants assert that obviousness requires that the prior art relied upon fairly teach or suggest all the elements of the instant invention and that an incentive or motivation be present in the prior art to produce the claimed invention with reasonable expectation of success in its production. The Applicants have shown that cited prior arts do not teach or suggest all the elements of the present invention, nor do they provide an incentive or motivation to produce the claimed invention with reasonable expectation of success in its production. Hence, the subject matter of the present invention is not

obvious to one with ordinary skill in the art at the time the invention was made. Accordingly, based on the above-mentioned remarks, amendment and cancellation of claim 2, Applicants respectfully request that the rejection of claims 1-2 and 5 under 35 USC 103 be withdrawn.

This is intended to be a complete response to the Office Action mailed March 2, 2004. Applicants submit that the pending claims are in condition for allowance. If any issues remain, please telephone the undersigned attorney of record for resolution.

Respectfully submitted,

Date: May 11, 2004

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